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Theoretical Study on Glycosyl Group Effect on Antioxidant Ability of Chrysin Bioflavonoid

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Antioxidants are compounds which can prevent biological and chemical substances from oxidative damage by reactive oxygen species. Flavonoids are the most important class of polyphenolic compounds that because of their antioxidant characters possess biological activities and pharmacological effects. Chrysin-6-C-fucopyranoside and chrysin-3-malonyl-6-C-fucopyranoside are mono C-glycosyl derivatives of chrysin and flavonoid metabolites in leaves of Cyclanthera pedata. In order to study the effect of glycoside group on the antioxidant ability of chrysin, theoretical parameters including bond dissociation enthalpy (BDE), energy gap (ΔE) and spin density for three above mentioned flavonoids are calculated using DFT method at the B3LYP/6-311++G** level in gas phase. In order to consider the various environments, solvent effects in water and DMSO using self-consistent reaction field (SCRF) and the polarizable continuum model (PCM) at B3LYP/6-311++G** level are performed. Obtained results show that solvent is able to cause significant change in the reaction enthalpies but no significant change on energy gap (ΔE) and spin density.

Our results indicate that BDE values due to its space prevention and presence of intra hydrogen bond between O atom of glycoside group (O-C1gg) in chrysin derivatives and 7OH have a low inverse effect on the BDE and so on antioxidant ability. We use Bader's atoms in molecules (AIM) theory to perform a topological study on chrysin and its derivatives to emphasize the presence of intra hydrogen bonds. Base on AIM analyses, these hydrogen bonds have covalent nature. Energy gap (ΔE) and spin density of flavonoid radicals almost do not change in the presence of glycoside group in gas phase, as well as in water and DMSO solvents. So, linked glycoside agent to chrysin does not improve its antioxidant ability.

Keywords: Antioxidant, Bond dissociation enthalpy (BDE), Energy gap (ΔE), Glycoside group

INTRODUCTION

Antioxidants are our first wall of defense against free radical damage. Overall, free radicals have been participated in the pathogenesis of 50 diseases [1]. When the required antioxidants for body is sufficient, this disorder of free radical becomes minimum and is so important for maintaining optimum health and wellbeing. So, knowing and consuming better antioxidants as dietary supplement or drug seem vital for helping to our body.

Flavonoids are an important class of antioxidants, possessing anti-cancer, anti-inflammatory, antibacterial, antiviral, and anti-allergic properties which are a consequence of their antioxidant character [2-4]. Existence of more than 4000 flavonoids makes classification of flavonoids, based on their structures, unavoidable. Previous studies indicated that there are direct relationship between antioxidant ability and structural details of flavonoids. For example, the presence of the hydroxyl groups in ring A and C for monohydroxy flavones [7] or C2-C3 double bond in C ring for taxifolin [8] or C=O group in 4 position in C ring for three flavonoids, catechin, quercetin and diosmetin,[9] leads to increase the antioxidant ability. Computational chemistry methods are one of the most important tools to

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gain advancement in this field, and several studies may be found in the literature [10,11].

To theoretically study the effect of glycoside group on antioxidant ability, chrysin and its two glycoside derivatives, chrysin-6-C-fucopyranoside and chrysin-3-malonyl-6-C-fucopyranoside, are selected.

Chrysin (5,7-dihydroxyflavone), shown in Fig. 1, is one of the flavonoids extracted from the Indian trumpet tree (Oroxylum indicum), and passion flower (Passiflora incarnata) [12]. Chrysin is also found in Elaeagnus angustifolia [13], fruit skin [14], honey and propolis [15]. Similar to other flavonoids, chrysin has many biological activities and pharmacological effects [16]. Chrysin-6-C-fucopyranoside Fig. 2a and Chrysin-3-malonyl-6-C-fucopyranoside Fig. 2b are flavonoids in leaves of Cyclanthera pedata which are found in South America and are considered for their anti-inflammatory, hypoglycaemic and hypocholesterolaemic properties [17]. Chrysin-6-C-fucopyranoside has fucopyranosyl group in C(6) position of chryin in comparison to chrysin. Chrysin-3-malonyl-6-C-fucopyranoside, as a chrysin derivative, accompanied by fucopyranosyl group in C(6) position has a malonyl agent which is an electron-withdrawing group (EWG).

In the present work, a theoretical study is carried out to investigate the effect of glycoside group on chrysin antioxidant ability by calculating three theoretical parameters, BDE, ΔE and spin density of chrysin and corresponding derivatives. Due to possibility of the formation of intra hydrogen bond in this type of structurs influenced on antioxidant ability, AIM theory is used to clarify it. To find the most stable structure all important dihedral angels are scanned like O1-C2-C1'-C2' and C7-C6-C1gg-Ogg as Figs. 1 and 2. Geometrical analysis of chrysin, chrysin-6-C-fucopyranoside and chrysin-3-malonyl-6-C-fucopyranoside rotamers shows that all of them are non-planar. It means that the dihedral angle between the AC bicycle and the B ring is different from zero. The most stable rotamer of these structures is presented in Figs. 1 and 2. All species necessary to study are generated from the most stable conformation of chrysin and its derivatives [18].

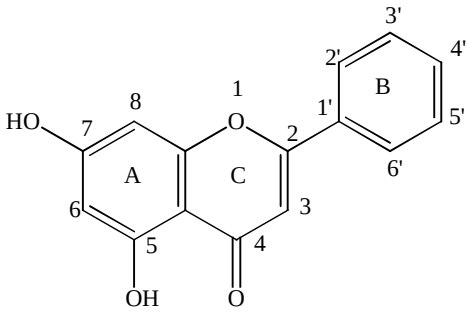

Fig. 1. Chemical structure of Chrysin with numbering for some key atoms.

COMPUTATIONAL DETAILS

All calculations are carried out using Gaussian program series 2003 [19] as basic program and Gaussian Viewer [20] as graphical medium. The optimization of the geometries is performed by employing a hybrid Hartree-Fock-density functional scheme, the adiabatic connection method-Becke three-parameter with Lee-Yang-Parr (B3LYP) functional of density functional theory (DFT) [21] with the standard 6-311++G** basis set. Full optimizations of all flavonoid structures and their radicals are performed without any symmetry constrains. The harmonic vibrational frequencies are calculated to confirm that an optimized geometry correctly corresponds to a local minimum which has only real frequencies.

The AIM analysis is performed with the AIM2000 code [22] with all default options. Integration of atomic properties over the atomic basins is performed in natural coordinates.

Theoretical Parameters

Calculation of bond dissociation enthalpy (BDE). A theoretical, quantum chemically determined, suitable parameter for describing the abstraction of a hydrogen radical from O-H bond of flavonoid is the bond dissociation enthalpy (BDE). BDE is the difference in heat of formation between flavonoid (FLOH) and its corresponding radical ($FLO^{\bullet}$). The BDE is equal to $H_r + H_h - H_p$ where H_r is the enthalpy of the radical generated by H-abstraction, H_h is the enthalpy of the H atom, and H_p is the enthalpy of the parent molecule, according to reaction 1.

$$FLOH + {}^{\bullet}OH \rightarrow FLO^{\bullet} + H_2O \quad (1)$$

The formed $FLO^{\bullet}$ radical must be relatively stable, so

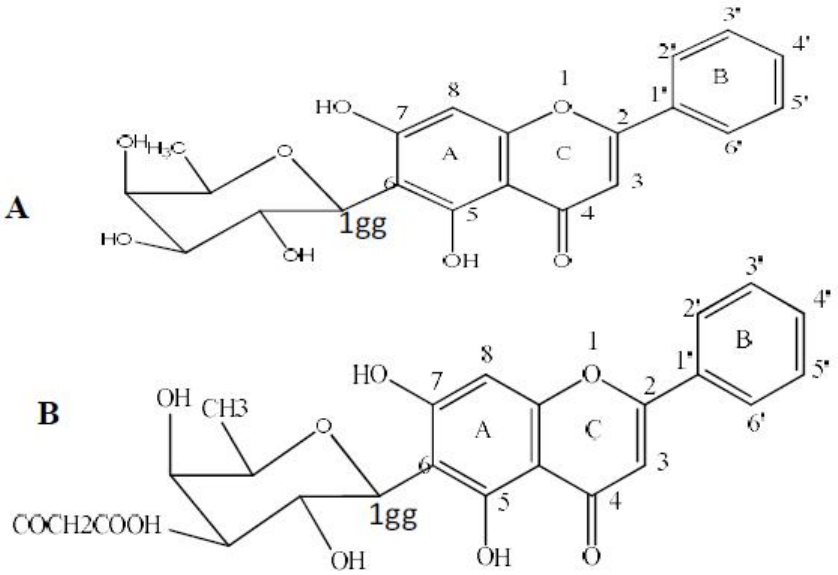

Fig. 2. Chemical structure of: A: chrysin-6-C-fucopyranoside, B: chrysin-3-malonyl-6-C-fucopyranoside. (1gg = C1 glycoside group).

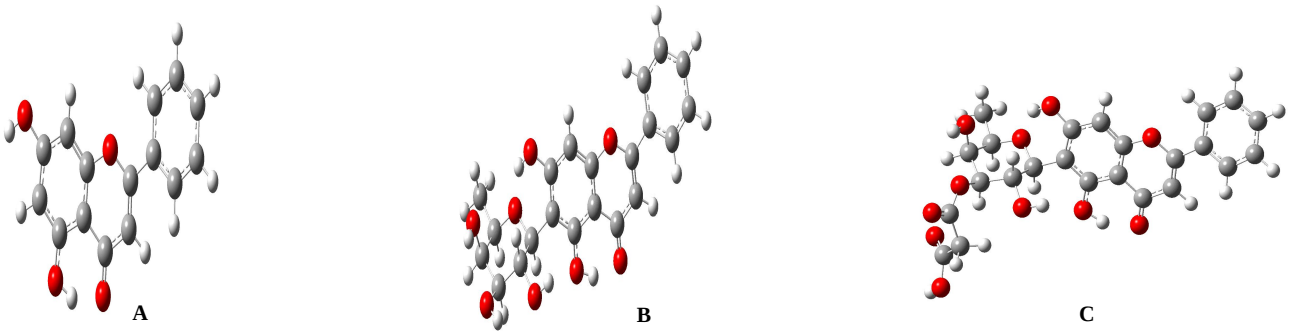

Fig. 3. Optimized structure of A: chrysin, B: chrysin-6-C-fucopyranoside, and C: chrysin-3-malonyl-6-C-fucopyranoside in gas phase at B3LYP/6-311++G** level.

this reaction is thermodynamically favorable. BDE values are corrected by taking in to account the zero point energy and the contributions from translational, rotational, and vibrational degrees of freedom in the heat of reaction at 298 K. The minimal value of the bond dissociation enthalpy (BDE) of OH bonds in flavonoids indicates that OH group on the flavonoid core possess the most abstractable hydrogen which OH group is targeted for radical attack.

DFT [23-26] calculations have been successfully used for computing O-H BDEs for phenolic compounds. The lower BDE value, the more efficient antioxidant ability.

Calculation energy gap (E_{LUMO} - E_{HOMO}). High value of E_{HOMO} is the tendency of the molecule to donate electrons to a suitable acceptor that is the lowest empty molecular orbital. The energy gap, ΔE (E_{LUMO} - E_{HOMO}), is the function of flavonoid reactivity towards the free radical [27]. Lower values of the energy difference will lead to good antioxidant efficiency.

Spin densities. Spin density of flavonoid is the third important factor in the determination of the antioxidant ability [28]. Spin density of neutral molecule is zero because this molecule does not have singlet electron. The

more delocalized the spin density in the radical of flavonoid, the easier formation of radical, and thus the lower value of BDE [29] so the antioxidant ability is more. Spin density delocalization means that the spin share of each atom is less as much as possible until spin density is distributed in the whole molecule.

AIM Analyses

The AIM theory has provided a powerful tool to define what is atom, and what is a bond in a quantum calculation of a molecular structure [30]. The reader is referred to ref. 25 for the proper definition of bonding, bond paths, critical points on the basis of electronic density $\rho_{(r)}$, and its gradient Laplacian. Briefly, interatomic interactions such as hydrogen bonds (HBs) can be described by the topological properties of the electron density $\rho_{(r)}$ at the (3, -1) bond critical point (BCP). The value of the density $\rho_{(r)}$ at the BCP for hydrogen bonds must be between 0.2×10^{-2} a.u. and 3.5×10^{-2} a.u., and the value of the Laplacian of the density at the BCP must be between 2.4×10^{-2} a.u. and 13.9×10^{-2} a.u. [31]. These mention values are slightly different for hydrogen bonds whit covalent nature [32-33].

RESULTS AND DISCUSSION

BDE Values of the Optimized Structures of Flavonoids

Chrysin structure, with its two derivatives, and their radicals are fully optimized at B3LYP method using 6-311++G** basis set with no initial symmetry restrictions and assuming C1 point group. Figure 3 shows the optimized structure of chrysin and its C-glycoside derivatives. Since these compounds have two suitable hydroxyl groups for hydroxyl free radical attack, geometry optimizations of the radicals are performed in the gas phase, water , and DMSO after H-atom is removed from the positions 5 and 7 with UB_3LYP/6-311++G** method. Results of the calculated 5OH and 7OH BDEs for chrysin, chrysin-6-C-fucopyranoside, and Chrysin-3-malonyl-6-C-fuco-pyranoside are listed in Table 1. For chrysin, the BDE value in 7OH in gas phase, 86.3 kcal mol^{-1}, is lower than 5OH, 97.82 kcal mol^{-1}, because 5OH position participates in inter hydrogen bond so 7OH of chrysin is more suitable for OH radical attack. For chrysin, in water and DMSO environments, 7OH is also more suitable for radical attack because the BDE value of 7OH in these two solvents is lower than that of 5OH. In chrysin-3-malonyl-6-C-fucopyranoside, this arrangement is still obtained in gas phase, however difference between two positions is lower, about 2.55 kcal mol^{-1}. In Table 2, distances of hydrogen bonds in three compounds are reported in gas phase, water, and DMSO. Generated intra hydrogen bond between H(O-C7) chrysin moiety and O-C1glycosid group (C1gg), glycoside moiety, leads to increase the BDE value in 7OH relative to chrysin from 86.31 to 91.59 kcal mol^{-1} in gas phase. The intra hydrogen bond between H(O-C7) and O-C1glycosid group (C1gg) in chrysin-6-C-fucopyranoside is stronger than another derivative of it according to its shorter intra hydrogen bond distance. This length in chrysin-6-C-fucopyranoside and chrysin-3-malonyl-6-C-fucopyranoside is 1.81 and 1.83 A°, respectively, in gas phase. For this reason the BDE value of OH7 in chrysin-6-C-fucopyranoside is greater than that of the OH7 position of chrysin. In Table 2, hydrogen bond distance of O (C4)---H(O-C5) for chrysin and its derivatives in solvents changes about 0.01 A° , but the hydrogen bond distance between chrysin moiety and glycoside moiety in OH7 position in solvents changes about 0.03 A° for chrysin-6-C-fucopyranoside and 0.02 A° for chrysin-3-malonyl-6-C-fucopyranoside.It means that H(O-C7)---O(C1gg) bond is more influenced by solvents. In Table 1, BDE values for two OH positions in solvent indicate that two OH groups for derivatives of chrysin are nearly equal in terms of antioxidant ability because two positions in its derivatives have intra hydrogen bonds. So, antioxidant activity of chrysin in the presence of glycoside group seems a little worse. For example, the BDE values in water for OH7 are 87.43, 91.31 and 91.05 kcal mol^{-1}, respectively, for chrysin, chrysin-6-C-fucopyranoside, and chrysin-3-malonyl-6-C-fucopyranoside.

Results of Energy Gap Calculations (E_{LUMO} - E_{HOMO})

HOMO and LUMO energies and their ΔE values of three flavonoids is presented in Table 3 in gas phase, water, and DMSO at the B3LYP/6-311++G** level. Our results indicated that these quantities are nearly fixed in gas phase. Figure 4 presents HOMO and LUMO orbitals of these

Table 1. Calculated 5OH and 7OH BDEs (kcal mol^{-1}) for Chrysin and Its Derivatives in Gas Phase, Water and DMSO at B3LYP/6-311++G** Level

OH Position	Chrysin	Chrysin-6-C-fucopyranoside	Chrysin-3-malonyl-6-C-fucopyranoside
Gas phase			
7OH	86.31	102.18	91.59
5OH	97.82	93.64	94.14
Water			
7OH	87.43	91.31	91.05
5OH	93.43	91.65	91.82
DMSO			
7OH	87.45	91.34	91.10
5OH	93.24	91.70	91.90

Table 2. Bond Distance (A°) of Optimized Structures of Chrysin and Its Derivatives in Gas Phase, Water and DMSO at B3LYP/6-311++G** Level

Bond distance (A°)	Chrysin	Chrysin-6-C-fucopyranoside	Chrysin-3-malonyl-6-C-fucopyranoside
Gas phase			
H-O(C5)	0.99	1.00	1.00
O(C4)---H(O-C5)	1.70	1.67	1.66
H-O(C7)	0.96	0.98	0.98
H(O-C7)---O(C1gg)	-	1.81	1.83
Water			
H-O(C5)	0.99	1.00	1.00
O(C4)---H(O-C5)	1.69	1.66	1.65
H-O(C7)	0.96	0.98	0.98
H(O-C7)---O(C1gg)	-	1.78	1.81
DMSO			
H-O(C5)	0.99	1.00	1.00
O(C4)---H(O-C5)	1.69	1.66	1.66
H-O(C7)	0.96	0.98	0.98
H(O-C7)---O(C1gg)	-	1.78	1.81

Table 3. HOMO and LUMO Calculated Energy Values (a.u.) of Chrysin and its Derivatives and their Energy Gaps ($\Delta E = E_{LUMO} - E_{HOMO}$) (kcal mol^{-1}) in Gas phase, Water and DMSO at B3LYP/6-311++G** Level

Energy	Chrysin	Chrysin-6-C-fucopyranoside	Chrysin-3-malonyl-6-C-fucopyranoside
Gas phase			
HOMO	-0.2363	-0.2367	-0.2404
LUMO	-0.0847	-0.0863	-0.0891
ΔE	95.13	94.41	94.93
Water			
HOMO	-0.2395	-0.2398	-0.2407
LUMO	-0.0855	-0.0865	-0.0871
ΔE	96.62	96.23	96.40
DMSO			
HOMO	-0.2394	-0.2397	-0.2407
LUMO	-0.0855	-0.0864	-0.0871
ΔE	96.59	96.23	96.40

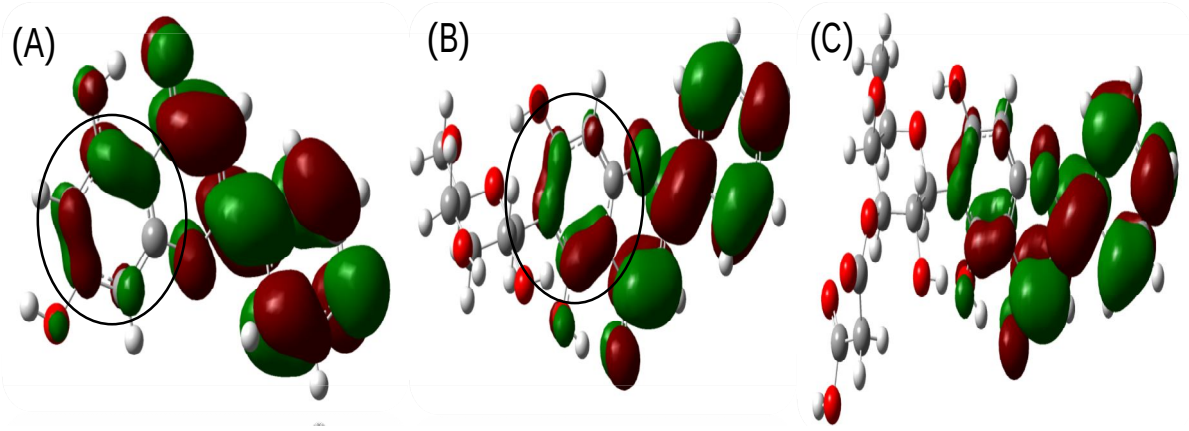

Fig. 4. HOMO and LUMO orbitals of A: chrysin, B: chrysin-6-C-fucopyranoside, and C: chrysin-3-malonyl-6-C-fucopyranoside in gas phase at B3LYP/6-311++G** level.

Table 4. Mulliken Atomic Spin Densities of Chrysin Radicals and Chrysin Derivative Radicals in Gas Phase, Water and DMSO at B3LYP/6-311++G** Level; (A: Chrysin, B: Chrysin-6-C-fucopyranoside, and C: Chrysin-3-malonyl-6-C-fucopyranoside)

The atom position	OH5 of A radical	OH5 of B radical	OH5 of C radical	OH7 of A radical	OH7 of B radical	OH7 of C radical
Gas phase						
O1	0.0130	0.0185	0.0183	0.0048	0.0038	0.0045
O(C5)	0.3705	0.3190	0.3138	-0.0181	-0.0178	-0.0168
O(C7)	-0.0122	-0.0169	-0.0166	0.4239	0.3876	0.3854
O(=C4)	0.0148	0.0084	0.0093	0.0613	0.0604	0.0590
C2	0.0005	-0.0043	-0.0042	0.0102	0.0155	0.0147
C3	0.0296	0.0341	0.0297	0.0193	0.0068	0.0107
C6	0.3704	0.3651	0.3504	0.2619	0.2820	0.2712
Water						
O1	0.0224	0.0258	0.0256	0.0084	0.0090	0.0097
O(C5)	0.3206	0.2883	0.2833	-0.0132	-0.0094	-0.0080
O(C7)	-0.0127	-0.0157	-0.0150	0.3722	0.3490	0.3459
O(=C4)	0.0034	0.0009	0.0015	0.0440	0.0406	0.0395
C2	-0.0016	-0.0052	-0.0048	0.0128	0.0177	0.0168
C3	0.0424	0.0443	0.0401	0.0381	0.0275	0.0313
C6	0.3653	0.3571	0.3407	0.2102	0.2071	0.1983
DMSO						
O1	0.0223	0.0256	0.0255	0.0083	0.0089	0.0097
O(C5)	0.3214	0.2889	0.2838	-0.0133	-0.0095	-0.0081
O(C7)	-0.0127	-0.0158	-0.0151	0.3731	0.3497	0.3466
O(=C4)	0.0035	0.0009	0.0016	0.0443	0.0409	0.0398
C2	-0.0015	-0.0052	-0.0048	0.0128	0.0177	0.0168
C3	0.0422	0.0441	0.0399	0.0378	0.0271	0.0310
C6	0.3655	0.3573	0.3409	0.2112	0.2082	0.1994

Table 5. The Selected Topological Parameters of A: Chrysin, B: Chrysin-6-C-fucopyranoside, and C: Chrysin-3-malonyl-6-C-fucopyranoside in a.u.

Position of Critical Point (3, -1)	Chrysin		Chrysin-6-C-fucopyranoside		Chrysin-3-malonyl-6-C-fucopyranoside	
	ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$
Gas phase						
H(OH5)-O(C4)	0.044	-0.044	0.052	-0.035	0.053	-0.035
H(OH7)-O(C1gg)	-	-	0.035	-0.031	0.034	-0.030

compounds in gas phase. Focusing on Fig. 4 indicates that range of HOMO and LUMO in the mentioned flavonoids is nearly equal. It means that glycoside group does not affect the energy of frontier orbitals, so this agent has neither increasing nor decreasing effect on antioxidant ability. In solvent, energy of HOMO is decreased and consequently ΔE values are increased. In the presence of water or DMSO, ΔE values are nearly equal, about 96 kcal mol^{-1} for all of the flavonoids. Hence, in the presence of solvent, glycoside group does not influence on ΔE value of chrysin.

Results of Spin Densities

Table 4 shows results of Mulliken atomic spin densities of Chrysin radicals and Chrysin derivative radicals in gas phase, water and DMSO solutions at B3LYP/6-311++G**. The spin densities were calculated using optimized structures of the 6 radicals of flavonoids. Three first columns are spin density values of the radicals produced from removing of hydrogen atom of flavonoid from the OH5 position. Three second columns are these values of the radicals produced from removal hydrogen atom of the flavonoid OH7 position. An overall view of the table shows that the radicals of these flavonoids are more stable than free radicals, like OH radical in the present study; this is largely due to the low values of spin densities on the atoms.

Hence, these compounds are suitable for consuming as antioxidants. Focusing on three first and second columns of spin density values indicates that spin density values are nearly fixed. For example, spin density values on O(C5) are 0.3705, 0.3190 and 0.3138 for chrysin, chrysin-6-C-fucopyranoside, and chrysin-3-malonyl-6-C-fucopyranoside radicals, respectively. In water media, spin density of this position is 0.3206, 0.2883 and 0.2883 for chrysin, chrysin-6-C-fucopyranoside, and chrysin-3-malonyl-6-C-fucopyranoside radicals, respectively. This indicates that the presence of polar solvent leads to low changes on the delocalization of spin density and more stable radicals.

The Bader Theory Applied for the Analysis of H-Bonds

The calculated values of electron density, $\rho(r)$, and Laplacian of electron density, $\nabla^2\rho_{(r)}$, at the bond critical points (BCPs) at B3LYP/6-311++G** level of theory are listed in Table 5 for chrysin and its derivatives. The molecular graphs (including the critical points and bond paths) of all compounds are shown in Fig. 5. Almost for all systems, the values of $\rho(r)$ for BCPs are more than the values proposed for hydrogen bonds. For example, $\rho_{(r)}$ of H (OH7)-O (C1gg) position in chrysin-6-C-fucopyranoside and chrysin-3-malonyl-6-C-fucopyranoside are 0.035 and 0.034 a.u., respectively. It means that intramolecular H-bonds studied in OH7 belong to the strong ones so hydrogen bonds have a covalent nature [32,33]. In chrysin-6-C-fucopyranoside, H(OH5)-O (C4) position has stronger intra

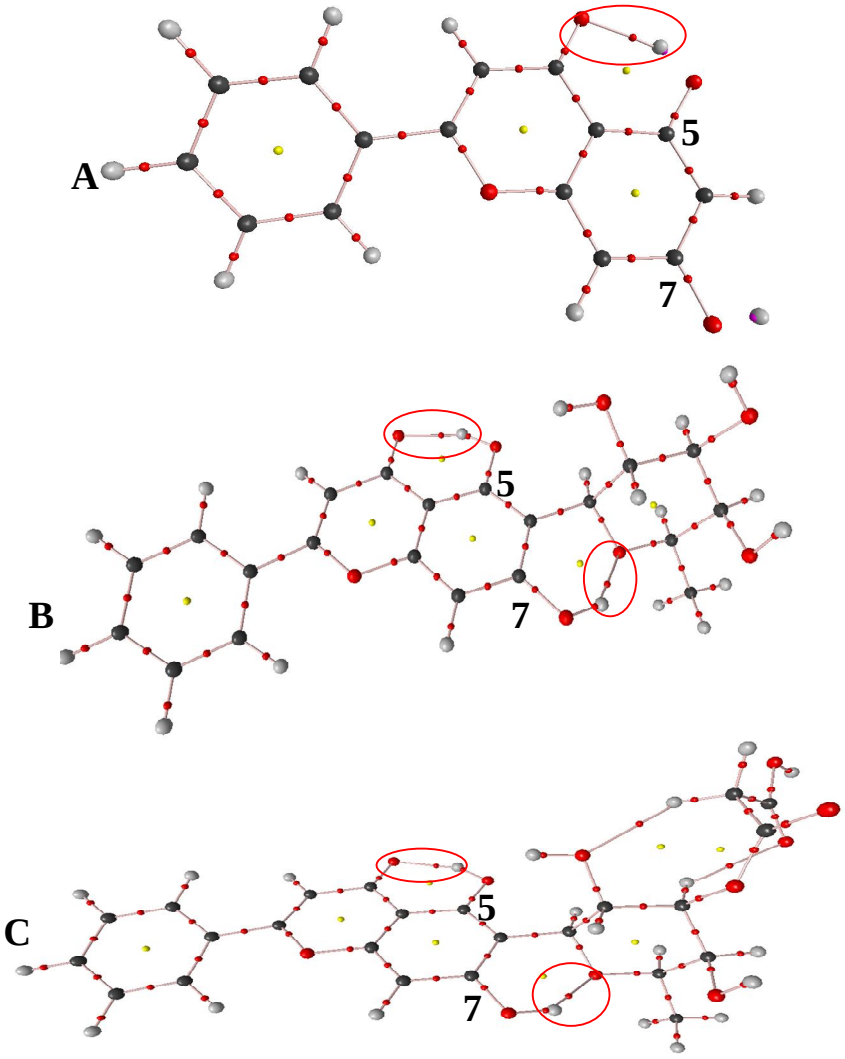

Fig. 5. Molecular graphs of A: chrysin, B: chrysin-6-C-fucopyranoside, and C: chrysin-3-malonyl-6-C-fucopyranoside. Nuclei and critical points (bond and ring) are represented by big and small circles, respectively.

hydrogen bond relative to H(OH7)-O (C1gg) position because ρ(r) values in two positions are 0.052 and 0.035, BDE values for these posit 574 ions are inverse, 93.64 and 102.18 kcal mol^{-1}. Focusing on chrysin-6-C-fucopyranoside in Fig. 2. indicates that space prevention in OH7 is greater than that in OH5. In two positions of chrysin-3-malonyl-6-C-fucopyranoside, ρ(r) values are the same and their BDE values are similar, 91.59 and 94.14 kcal mol^{-1}, respectively. It means that the significant effect is related to the space prevention.

CONCLUSIONS

In this work, BDE, ΔE and spin densities for chrysin, chrysin-6-C-fucopyranoside, and chrysin-3-malonyl-6-C-fucopyranoside are studied in gas phase, water, and DMSO. The results were obtained at B3LYP/6-311++G** level. The 7OH group is the most favored site for hemolytic O-H

breaking in chrysin in gas phase, water and DMSO. The DFT results indicate that the 5-OH group of chrysin is not involved in the antioxidant mechanism due to its higher BDE value, because this OH position has strong intra hydrogen bonds. In chrysin-6-C-fucopyranoside, favored site for hemolytic O-H breaking is 5OH position in gas phase, because the 7OH position has intra hydrogen bonds with glycoside group and space prevention in the position in gas phase. The 5OH position in chrysin-3-malonyl-6-C-fucopyranoside is found as favorable as 7OH position. ΔE for three flavonoids indicates that glycoside group does not affect ΔE value of antioxidant. Spin density results indicate that their radicals are the so more stable and glycoside group have no effect on the antioxidant ability.

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